REMARKS

The Office Action dated December 28, 2004, has been received and reviewed. Claims 1-4, 8-16, 20-27, 31-34, 37-42 and 47-51 are pending in this application. Claims 1-4, 8-16, 20-27, 31-34, 37-42 and 47-51 stand rejected. Applicants respectfully request reconsideration of the application as amended herein and in view of the remarks below.

I. Declaration

Applicants have included a corrected declaration from inventor Yuehua Li with this response.

II. Claim Amendments

Claim 1 has been amended to correct a grammatical error to include the word "or". Claim 3 has been amended in view of the restriction requirement. Claim 24 has been amended to include the recitations of Claim 31. Claims 49-51 have been amended to depend from Claim 1. Claims 2, 13 and 26 have been amended to recite that the active fragment inhibits the mediator. Claims 31-34, 37-42 and 47-48 have been canceled without prejudice or disclaimer.

III. New Matter Rejection

Claims 2, 13, 26, 33 and 48 stand objected to as purportedly raising new matter. Applicants respectfully disagree with this assessment. We note that the application discloses in the third full paragraph of the detailed description that "[t]he present invention also includes methods of reducing inflammation in a subject comprising the administration of a therapeutically effective amount of a compound that inhibits the MARCKS-related release of inflammatory mediators, whereby mucus secretion in the subject is reduced compared to that which would occur in the absence of said treatment." Furthermore, the specification in paragraph 16 notes that "[t]he active fragment is at least six amino acids in length. . . . [and a]s used herein, an "active fragment" of a MARCKS protein is one that affects (inhibits or enhances) the MARCKS protein-mediated release." However, in an effort to expedite prosecution of this matter, Applicants have amended Claims 2, 13 and 26 to track the language as recited in the specification. Accordingly, Applicants respectfully request

reconsideration to Claims 2, 13 and 26. Claims 33 and 48 have been canceled without prejudice thus mooting this rejection.

IV. Claim Objections

Applicants have amended Claim 1 to correct a grammatical error to include the word "or" as suggested by the Examiner. Accordingly, Applicants respectfully request that the objections to Claim 1 be withdrawn.

V. Claims Rejections – 35 U.S.C. § 112, First paragraph

Claims 1-4, 8-14, 20-27, 31-34, 37-42 and 47-51 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse these rejections due to the amendments to the claims and the reasons enumerated below.

Applicants note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Furthermore, the test for whether or not the enablement requirement has been met involves determining whether or not practice of the invention as claimed involves "undue experimentation". It has long been settled that "the key word is 'undue', not 'experimentation'". *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). Applicants submit that the current technology requires routine effort, and not undue experimentation.

Applicants note that the specification of the present application illustrates methods of inhibiting an inflammatory mediator as recited in Claims 1-4, 8-11, 24-27 and 49-51. In the specification the Applicants show that stimulated release of the inflammatory mediator myeloperoxidase (MPO) from human (FIG. 9) or canine (FIG. 10) neutrophils can be blocked in a concentration-dependent manner by the MANS peptide. Specifically, FIG. 9 shows

isolated neutrophils that were stimulated to secrete MPO. A concentration of 100 μM MANS peptide decreased secretion of MPO to control levels (* = $p<0.05$). This demonstrates that the MANS peptide can be used to inhibit inflammatory mediators. Because there is evidence that the MANS peptide can be used to inhibit inflammatory mediators Applicants submit that the specification contains an enabling disclosure. Paragraph 81 further shows that blocking the release of inflammatory mediators is one cellular secretory process. The present invention documents a secretory response in both NHBE cells and in neutrophils. *See*, paragraph 49. Therefore, Applicants submit that the enablement standard is satisfied in the present application. Thus, Applicants submit that the present rejection should be withdrawn. Accordingly, Applicants submit that the specification includes an enabling disclosure for Claims 1-4, 8-14, 24-27 and 49-51.

Furthermore, figures 11-15 show MPO secretion in response to secretagogues. Because secretagogues are also known to activate several protein kinases. The secretagogues can interact with airway epithelial (goblet) cells and activate two separate protein kinases, PKC and PKG. Activated PKC in turn phosphorylates MARCKS, causing MARCKS translocation from the plasma membrane to the cytoplasm, whereas PKG, activated via the nitric oxide (NO) → GC-S → cGMP → PKG pathway, in turn activates a cytoplasmic PP2A, which dephosphorylates MARCKS. This dephosphorylation stabilizes MARCKS attachment to the granule membranes. In addition, MARCKS also interacts with actin and myosin, thereby linking granules to the cellular contractile machinery for subsequent movement and exocytotic release. This dephosphorylation can allow MARCKS to regain its membrane-binding capability, enabling its attachment to membranes of cytoplasmic mucin granules. Accordingly, Applicants submit that the Application illustrates the regulation of mucin granules and the regulation of the exocytotic release of such mucin granules as recited in Claims 37, 39-40 and 42. As shown in FIGs. 3A-3C, the antisense oligonucleotide down-regulated MARCKS mRNA. Accordingly, Applicants further submit that Claims 37, 39-40 and 42 of the present application are enabled. Applicants note that they have canceled these claims without prejudice or disclaimer to expedite prosecution of this matter.

Applicants note that the specification in paragraph 16 notes that "[t]he active fragment is at least six amino acids in length. . . . [and a]s used herein, an "active fragment" of a MARCKS protein is one that affects (inhibits or enhances) the MARCKS protein-mediated

release." Applicants note that one of skill in the art would be able to readily prepare a cell culture to test active fragments of the MARCKS protein. Applicants note that they have provided one specific fragment, the MANS peptide, SEQ ID NO. 1 which illustrates such a fragment. Accordingly, Applicants submit that the specification provides guidance to one of skill in the art to make such a fragment. Accordingly, Applicants respectively request reconsideration and withdrawal of the rejections to the claims.

Additionally, under the 35 U.S.C. 112, first paragraph rejection, the Office Action alleges that the state of the art is highly unpredictable and that there are no working examples in the specification. Applicants note that one of skill in the art would be able to readily predict the ability to modulate neutrophils, basophils, eosinophils, monocytes or leukocytes. Applicants note that an enhanced secretory response to PMA alone was documented in NHBE cells (FIG. 1, *column 4*) and in neutrophils (FIG. 11). Furthermore, blocking antibodies have been demonstrated as useful therapies against inflammation in the neutrophil-associated tissue injury in acute inflammation (Harada et al., 1996, Molecular Medicine Today 2, 482). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to the claims.

The Office Action also alleges that the claims are not enabled for *in vivo* therapeutic methods. Applicants respectfully submit that the *in vitro* data can be readily extrapolated to the *in vivo* methods claimed. Applicants present examples disclosed in the specification that relate to mucin secretion. As noted in the *Manuel of Patent Examining Procedure* (M.P.E.P.), "[c]ompliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed." M.P.E.P. § 2164.02. Moreover, M.P.E.P. § 2164.02 further states that "because only an enabling disclosure is required, applicant need not describe all actual embodiments." With respect to Applicants presentation of *in vitro* data, Applicants submit that one of ordinary skill in the art is provided enough information in the form of *in vitro* data to determine an *in vivo* method of treating inflammation in a subject, comprising administering an effective amount of a MANS peptide to a subject in need of such treatment. Applicants note that the normal human bronchial epithelial cell type and the nature of the experiments conducted are particularly suited for correlation of results obtained *in vitro* to results expected from *in vivo* experiments. Thus, the observed effects on the epithelial cells *in vitro* provide one of ordinary skill in the art the

tools to conduct routine experimentation to devise a treatment protocol for a subject in need of treatment as provided by the present application. Applicants note that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless there is evidence that the model does not correlate. *See*, M.P.E.P. § 2164.02; *See also, In re Brana* 51 F.3d 1560, 1566. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1-4, 8-16, 20-27 and 49-51.

Written Description

Claims 1-4, 8-16, 20-27, 31-34, 37-42 and 47-51 are also rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention. Applicants respectfully disagree with this assertion.

Applicants have amended the claims reciting said "active fragment of the MANS peptide comprises at least six amino acids" to include the recitation "and retains its ability to inhibit an inflammatory mediator". Applicants submit that one of skill in the art could readily draw up a list of six amino acids from the MANS peptide and prepare an assay to test the activity of each fragment. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1-4, 8-16, 20-27 and 49-51.

Additionally, Applicants note that the U.S.P.T.O. has clarified the standard for examining applications for compliance with respect to the written description requirement of 35 U.S.C. §112, first paragraph. These guidelines state, in part:

> The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed . . .. Consequently, rejection of an original claim for lack of written description should be rare.

(Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1105 (Jan. 5, 2001); emphasis added). Applicants respectfully contend that the specification does provide a sufficient written description so that one skilled in the art would appreciate that the Applicant was in possession of the claimed invention at the time of filing. Adequate written support does not require that the application contain an exhaustive enumeration of all possible peptide fragments. Applicants submit that a person of skill in the art can readily envision fragments comprising the amino acid sequence of SEQ ID NO. 1. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph to the pending Claims.

VI. Claims Rejections – 35 U.S.C. § 103(a)

A. Adler et al (CHEST. May, 2000)

Claims 1-2, 8-11, 12-14, 20-27, 31-34, 37-42, 47-48 and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Adler et al (CHEST. May, 2000), (hereinafter "Adler"). Applicants traverse this rejection for the reasons set forth below.

To establish a prima facie case of obviousness, the prior art reference or references when combined must teach or suggest *all* the recitations of the claim, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). To support combining references, evidence of a suggestion, teaching, or motivation to combine must be clear and particular, and this requirement for clear and particular evidence is not met by broad and conclusory statements about the teachings of references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The Court of Appeals for the Federal Circuit has also stated that, to support combining or modifying references, there must be particular evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir.

2000). Furthermore, as recently affirmed by the Court of Appeals for the Federal Circuit in *In re Sang-su Lee*, a factual question of motivation is material to patentability, **and cannot be resolved on subjective belief and unknown authority**. *See In re Sang-su Lee*, 277 F.3d 1338 (Fed. Cir. 2002). Respectfully, as will be discussed below, the Official Action fails to meet the requirements for a prima facie showing of obviousness under § 103.

Applicants note that the present invention relates to methods of inhibiting **inflammatory mediators released from inflammatory cells** and **not epithelial cells** as recited in Adler. Applicants submit that it is well known in the art that **epithelial cells and inflammatory mediators are different** from one another. Applicants submit that it is known that a wide variety of agents and inflammatory/humoral mediators can provoke mucin secretion. These include cholinergic agonists, lipid mediators, oxidants, cytokines, neuropeptides, ATP and UTP, bacterial products, neutrophil elastase, and inhaled pollutants. Applicants further note that epithelial cells and inflammatory cells have very different responses to exogenous stimuli and can have different biochemical signaling pathways. Thus, it would not be expected from this publication that inflammatory cells would behave similarly to epithelial cells. Accordingly, Applicants respectfully submit that Adler does not teach or suggest the present invention. There is nothing in this publication, which would make the present invention obvious. Applicants submit that this reference fail to contain any motivation to combine their teachings as required by *In re Sang-su Lee*. Furthermore, even if Adler was combined with another publication, one would not arrive at the present invention as it relates to inflammatory mediators. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections to Claims 1-4, 8-16, 20-27 and 49-50.

B. U.S Patent No. 6,506,779

Claim 51 also stands rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 6,506,779 in view of Adler. Applicants submit that the '779 patent relates to acetylene derivatives, methods of treatment and pharmaceutical compositions for the treatment of cyclooxygenase mediated diseases. It does not in any way discuss or even contemplate the MANS peptide or a MARCKS related protein. Accordingly, for the reasons stated above and in this section, Applicants submit that the '779 patent and Adler either alone or in combination fail to contain any motivation to combine their teachings as required by *In re*

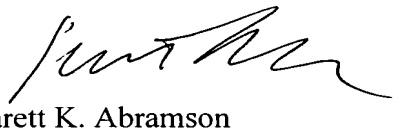
Sang-su Lee. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection to Claim 51.

CONCLUSION

In view of the remarks presented herein, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully submitted,



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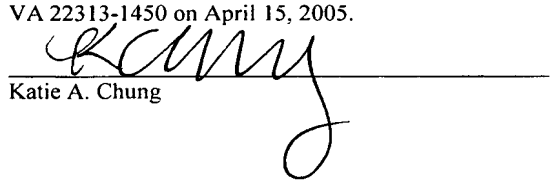

Katie A. Chung